Parkinson's disease and parkinsonisms: imaging

L. Curatola
C. Paci
R. Gobbato
T. Carboni
G. D'Andreamatteo
S. Sobrini
V. Urbano
A. Brandimarti
S. Sanguigni

Department of Neurology, "Madonna del Soccorso Hospital", San Benedetto del Tronto (AP), Italy
E-mail: luicura2@fastwebmail.it

Parkinson's disease (PD) is a neurodegenerative disorder that affects 3% of the general population. It is the second most common neurological cause of disability and, evolving over decades, has a major and increasing impact on quality of life. The causes of PD are not known, but it is thought that environmental and genetic factors may play an important role. In particular, the neurodegenerative process mainly involves the neurons of the ventrolateral portion of the substantia nigra pars compacta, while there is less involvement of the ventromedial and dorsal portions. This leads to a corresponding loss of dopaminergic terminals, above all in the caudal part of the putamen, followed by loss of those in the rostral portion of the putamen, and in the caudate nucleus. It is now established that the motor symptoms of the disease appear when loss of the dopaminergic neurons in the substantia nigra reaches around 70-80% of the total. Clinically, PD is characterised by the classic motor picture of resting tremor, rigidity, bradykinesia and postural instability. The basal ganglia can be seen as a sort of modulatory circuit regulating the flow of information from the cerebral cortex to the motor neurons of the spinal cord. The overall effect of reduced dopaminergic stimulation in PD is significantly increased inhibition of the substantia nigra pars reticulata and medial globus pallidus and thalamus and, as a result, reduced excitation of the motor cortex. According to Braak's hypothesis, substantia nigra damage is always accompanied by extensive **extranigral neurodegeneration**, which extends to the dorsal motor nucleus of the glossopharyngeal nerve and vagus nerve, the intermediate reticular area, some of the nuclei of the reticular formation and of the raphe, the locus coeruleus-subcoeruleus complex, the magnocellular nucleus, and other nuclei of the thalamus and amygdala. This would explain the onset of the non-motor symptoms complex of PD, which can often precede the diagnosis by a number of years. The term parkinsonisms covers a number of syndromes, including some that are more specifically referred to as atypical parkinsonisms, namely, multisystem atrophy, progressive supranuclear palsy and corticobasal degeneration, but differential diagnosis of PD also considers dementia with Lewy bodies, vascular parkinsonism, iatrogenic parkinsonism and essential tremor. Diagnosis is not always straightforward and is often delayed. However, in recent years imaging techniques have become increasingly refined, thanks both to the advent of new instruments and to the evolution of traditional methods. In a brief overview of the parkinsonisms, it can be recalled that **multisytem atrophy (MSA)** is a sporadic, adult-onset neurodegenerative disease of undetermined aetiology, characterised by parkinsonism and cerebellar, autonomic and pyramidal disorders in various combinations. The disease, which is highly variable, is associated with neuronal loss and gliosis of the substantia nigra, striate, pons, cerebellum and Onuf's nucleus. There are two forms: MSA-p (striatonigral degeneration with prevalence of parkinsonian symptoms) and MSA-c (olivopontocerebellar atrophy with prevalence of cerebellar signs). Autonomic and urinary disorders (orthostatic hypotension, urinary incontinence) are present in both cases. The term Shy Drager syndrome, which indicated a form with predominantly autonomic symptoms, is no longer used. The clinical picture of **progressive supranuclear palsy (PSP)** is characterised by supranuclear ophthalmoplegia, neck dystonia, parkinsonism, pseudobulbar palsy, postural instability with frequent falls and frontal-type dementia. **Corticobasal degeneration**, in which there is contemporaneous involvement of the cerebral cortex (mainly frontal and parietal) and of the basal ganglia (in particular the striatal basal ganglia), is characterised by the presence of an asymmetrical akinetic-hypertonic and dystonic picture and apraxia, cortical sensory disturbances

(double-stimulus extinction, impaired graphaesthesia), focal reflex or action myoclonus and, more rarely, the strange phenomenon of alien hand syndrome. **Dementia with Lewy bodies** is a very common subgroup after Alzheimer's disease.
These patients often present symptoms typical of parkinsonism: rigidity and bradykinesia, hypophonia, masked facies, camptocormia and slow gait; tremor is often absent. Differential diagnosis versus Parkinson's disease with dementia depends on the timing of the extrapyramidal and cognitive symptoms: current consensus is to diagnose dementia with Lewy bodies only if dementia develops within 12 months of the onset of motor symptoms.
As regards **imaging techniques**, it must immediately be pointed out that the morphological and densitometric characteristics of the nigrostriatal structures rarely point to a specific diagnosis of degenerative disease; therefore, neuroradiological techniques (CT and MRI) have, to date, been used to exclude underlying vascular or neoplastic diseases. However, radiological signs considered typical of some forms have been described: atrophy of the cranial mesencephalon in PSP, "knife edge" thinning of the postcentral gyrus in corticobasal degeneration, cruciform hyperintensity of the pons and atrophy of the pons in MSA-c, and hyperintensity of the lateral edge of the putamen in MSA-p. However, these abnormalities are not present in all patients with MSA and some of them, such as the hyperintensity of the lateral edge of the putamen, are not specific for this disease, given that they can also be observed in subjects with PD.
Recently, Quattrone's group, using 1.5-T MRI to measure the transverse diameter of the middle cerebellar peduncles (MCPs) in patients with MSA, patients with PD and healthy controls, showed (by means of a special technique – morphometric MRI) that the MCPs were atrophic in MSA and that this measurement was useful for distinguishing subjects with MSA (both the MSA-p and the MSA-c forms) from those with PD. In conclusion, morphometric MRI of the MCPs could constitute, in the authors' view, a routine examination that might be used to distinguish, with 100% sensitivity and specificity, between patients with MSA and those with PD.
Despite these recent developments in the ambit of the traditional techniques, the imaging methods most frequently used in the diagnosis of PD belong to the sphere of **nuclear medicine**.
Brain PET and SPECT make it possible to study dopaminergic receptor density using radiopharmaceuticals of different types that act specifically at pre-synaptic (18F-DOPA, 123I-FP-CIT) and post-synaptic (18F-spiperone, 123I-IBZM) levels. SPECT with 123I-FP-CIT (ioflupane) has been found to be particularly sensitive in the differential diagnosis of parkinsonian disorders versus essential tremor, but also in iatrogenic and vascular parkinsonisms: this radiopharmaceutical has also shown high accuracy in confirming suspected dementia with Lewy bodies. Various studies have also suggested using post-synaptic receptor-specific radiopharmaceuticals (e.g. brain SPECT with 123I-IBZM) or, alternatively, investigating cardiac adrenergic receptor density (123I-MIBG) for the differential diagnosis of PD versus atypical parkinsonisms.

Transcranial sonography

The parenchyma, too, can be usefully studied through acoustic windows. In extrapyramidal disease it is particularly important to be able to insonate the mesancephalon with relative ease. First, the classic butterfly-shaped mesencephalon is insonated through the preauricular acoustic bone window in the axial planes. After this, the echogenicity of the substantia nigra, in the area of the mesencephalic peduncles, is identified. A recent study showed that increased echogenicity (hyperechogenecity) of the substantia nigra, visualised and measured using transcranial sonography, is not only a typical marker in more than 90% of patients with idiopathic PD, but can also be found in around 9% of healthy subjects with preclinical nigrostriatal system vulnerability. The same study demonstrated that the magnitude of this marker does not change during the course of the disease and that it is probably correlated with iron metabolism in affected subjects.
Another study showed characteristic alterations of the deep structures in the different clinical forms of idiopathic PD. Pronounced bilateral hyperechogenicity of the substantia nigra could indicate an early-onset rather than a late-onset PD and a rigid-akinetic or mixed form rather than a tremorigenic form. The degree of substantia nigra echogenicity is negatively correlated with age at onset of the disease, but remains stable during the course of it. Conversely, hyperechogenicity of the caudate nucleus increases with increasing duration of the disease and seems to be correlated with the incidence of dopaminergic treatment-induced psychosis, independently of PD duration. Hyperechogenicity of the lenticular nucleus points to a rigid-akinetic rather than a tremorigenic form of PD. Reduced echogenicity of the brainstem raphe is associated with depression.